On page 30, line 31:

C6 b) Synthesis of Boc-Trp-Phe-{(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-[2-(4-nitro-

REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 21-23, 25-27, 28 and 29 have been amended. The amendments are supported in the as-filed specification. The claims presently pending in the application are 21-33, inclusive.

The amendments made to the specification at page 2, lines 3-9 and page 5, lines 15-20 serve to overcome the 35 USC §112, first paragraph, rejections labelled d), g) and h). The withdrawal of the rejection is accordingly solicited.

It is respectfully submitted that the amendments made to claims 21 serve to overcome the §112, second paragraph, rejection labelled e), g), j), o), p), t), ah), ak), al), and au).

With respect to the rejection labelled s), the Examiner's reasoning is not understood. Perhaps, the Examiner has not taken into account the fact that by varying Ar, R_1 and R_2 can assume various meanings and, therefore, they can, indeed, be the same or different as indicated.

With respect to the rejection labelled y),3-pyridyl-methyl and 4-pyridyl-methyl are not substituents of the phenyl moiety. There are, however, other definitions for R_2. Accordingly, claim 23 has been amended to read "or are selected from the group consisting of 3-pyridyl-methyl and 4-pyridyl-methyl;".

The rejection labelled ae) is not clear. In all probability it is due to the fact that an incorrect structural formula was inadvertently included in claim 21 and formed the basis of the

rejection. The correct structural formula has now been added by this amendment. It should be noted that all of the disclosed and claimed compounds have X_3 = -CONH. (X_3 should be read as written in Formula 1.) In this connection, the Examiner should note that Suc means Succinyl (i.e., there are two carboxy residues, i.e., according to Figure 1, the substituents X_3 and X_4 both mean -CONH).

With respect to the rejection labelled af), it is probably based on a misunderstanding. According to claim 21, within the defined group is the group $-(CH_2)_rAr$, wherein r = 1 and Ar is 4-pyridyl. Thus, in naming compound xiii the simpler (and clearer nomenclature according to peptide chemistry) was used, i.e., Ala (alanine) substituted on the lateral chain (methyl) by the group 4-pyridyl, which is indicated in parentheses. Applicants wish to point out to the Examiner that the same nomenclature was used in respect of compounds ix, x and xi which was found to be acceptable by the Examiner.

With respect to the rejection labelled ag), the same explanation obtains as provided above in respect of af), except that 3-pyridyl is referred to instead of 4-pyridyl.

With respect to the rejection labelled an), it is analogous to the misunderstanding previously considered under the rejection labelled y). In fact, as can be seen in claim 21, R_9 is defined as $N(R_{11})CO(CH_2)_hR_{12}$, wherein R_{12} " ... piperidine optionally substituted with ... or 4-aminosulfonyl group ... piperazine optionally substituted on the N-atom by C_{1-3} alkyl ... ". This definition is obviously inconsistent with the rest of the application as a whole. In fact, the substituent "4-aminosulfonyl" must be present on piperazine and not on piperidine. As can be seen, when the preferred compounds are described and claimed (see page 7 and original claim 8), R_{12} is correctly defined as 4-aminosulfonyl piperazine, while no 4-aminosulfonyl piperidine

is present in any example. It is thus evident that in typing the claim, and the corresponding portion of the specification, that the substituent was attributed in error to piperidine instead of to piperazine.

The definition "4-hydroxy-cyclohexan-1yl-amino" derives from claim 21 when R_{12} is " ... an amino-cyclo-hexane optionally substituted by a hydroxy group".

With respect to the rejection labelled as), the explanation given above with respect to the rejection labelled an) also obtains.

The objection to the disclosure at page 8, item 5, with respect to the definitions of the variables, has been overcome by applicants having now provided the correct structural formula in the specification which is supported in the originally filed PCT application.

The missing text at page 30, line 31, has been supplied by an amendment to the specification.

The objection set forth at item 7 on page 9 of the Office Action under §132 has been overcome by deleting the moiety CN from the definition given for Ar_1 at page 1, lines 29-32.

The rejection under §112, first paragraph, set forth in item 8 at page 9 of the Action has been overcome by deleting CN from the definitions given for Ar_1 in claim 21.

Applicants respectfully traverse the §112, second paragraph, rejection of claims 21-24, 26, 28, 30, 32 and 33 in view of the amendments made to the claims.

With respect to item 9, a), the term "general" has been deleted from claim 21.

With respect to the rejection under item 9, b), claims 21, 32 and 33 have been amended by substitution of the correct structural formula.

The rejection under item 9, c) has been remedied by the substitution of the correct structural formula in claim 21.

The rejection under item 9, d) has been corrected by amending claim 21 appropriately.

The rejection under item 9, e) has been remedied by the substitution of the correct structural formula.

The amendments made to claim 21 serve to overcome the rejection under item 9, f).

With respect to item 9, h), "and" has been deleted between "tosyl" and "tetrahydropyranyl".

In claim 21, the word "and" between R_8 and R_9 is now in normal size letters and is no longer in subscript form.

With respect to item j), "on" has been substituted for "by".

In the rejection labelled k), "and" has been deleted from claim 22 and "C_{1-3}" has been inserted.

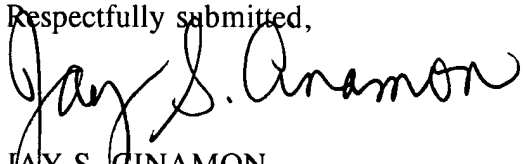
The comment with respect to k) above also applies with respect to l) herein.

It is respectfully submitted that all of the rejections and objections of record have been overcome and, accordingly, withdrawal is solicited and the issuance of a Notice of Allowance is respectfully requested.

Attached is a marked-up version of the specification and claims which have been amended.

Please charge any fees which may be due and which have not been submitted herewith to our deposit account No. 01-0035.

Respectfully submitted,



JAY S. CINAMON
Registration No. 24,156
Attorney for Applicant(s)

ABELMAN FRAYNE & SCHWAB
150 East 42nd Street
New York, New York 10017-5612
Tel. (212) 949-9022
Fax (212) 949-9190

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PATENT DOCKET 205.010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: ALTAMURA et al.

Serial No.: 09/762,522

Filed: — 02/05/01 —

For: MONOCYCLIC COMPOUNDS HAVING NK-2 ANTAGONIST ACTION AND COMPOSITIONS CONTAINING THEM

February 12, 2003

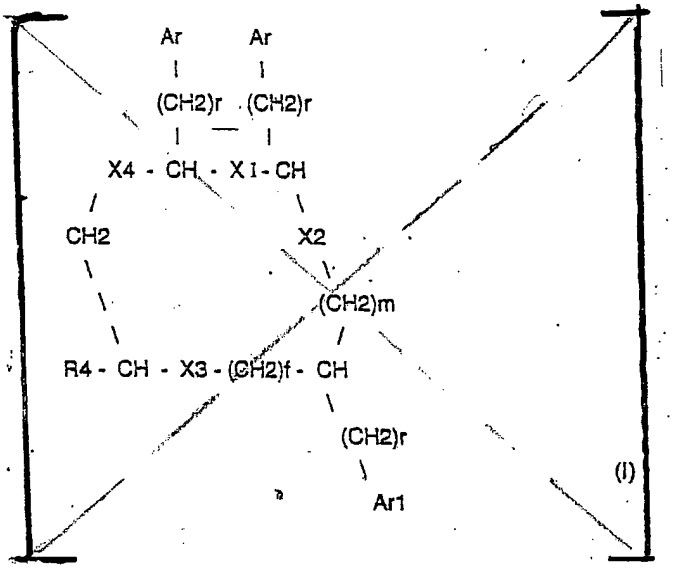
APPENDIX SHOWING CHANGES MADE

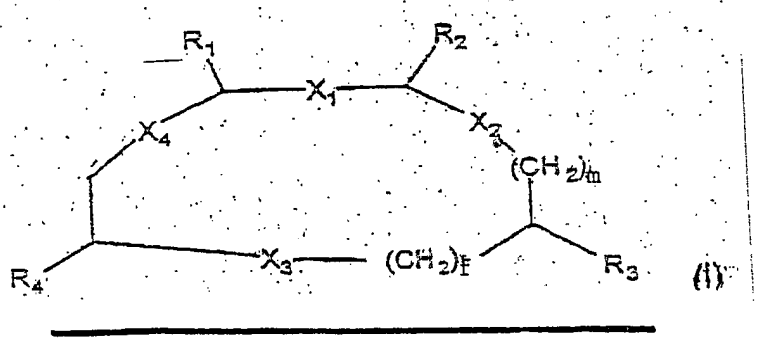
In the Claims

Claims 21-23, 25-27, 30 and 31 have been amended as follows:

--21. (Amended) Monocyclic compounds of [general] formula (I)

wherein:





X_1, X_2, X_3, X_4 are the same or different, and are selected from the group consisting of -CONR-, -NRCO-, -CH_2-NR-, and -NR-CH_2- where R is selected from the group consisting of H, C_{1-3} alkyl, and benzyl;

f[,] and m[,] are the same or different, and is a number selected from the group consisting of 0, 1 and 2;

R_1 and R_2, are the same or different, and represent:

-$(CH_2)_r$Ar where r is 0, 1 or 2 and Ar is an aromatic group selected from the group consisting of benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, optionally substituted with up to 2 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkyloxy, C_{2-4} amino-alkyloxy, halogens, OH, NH_2, CN, and NR_6R_7, where R_6 and R_7, same or different, are H or C_{1-3} alkyl,

R_3 is -$(CH_2)_r$$Ar_1$ where r is 0, 1 or 2 and Ar_1 is an aromatic group selected from the group consisting of benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzimidazole,

optionally substituted with up to 2 groups selected from the group[s] consisting of C_{1-3} alkyl, [and] C_{1-3} haloalkyl, C_{1-3} alkyloxy, [and] amino-alkyloxy, halogens, OH, NH_2, [CN] and NR_6R_7, where R_6 and R_7, same or different, are H or C_{1-3} alkyl,

R_4 is -NR_8R_9, where R_8 is H or C_{1-3} alkyl; and

R_9 is selected from the group consisting of methanesulfonyl, tosyl, [and] tetrahydropyranyl, tetrahydrothiopyranyl optionally mono or di-substituted by oxygen on the S atom, piperidyl, optionally substituted on the N-atom by a C_{1-3} alkyl, C_{1-3} acyl, aminosulfonyl, or

methanesulfonyl; or a group $-(CH_2)gR_{10}$ where g is 1,2, or 3 and R_{10} is selected from the group consisting of morpholine, furan and CN;

or $R_{8[and]}$ and R_9 together with the N atom to which they are linked form a piperazine optionally substituted at the other N atom substituted [on one of its nitrogens] by a C_{1-3} alkyl, C_{1-3} acyl or methanesulfonyl;

$-N(R_{11})CO(CH_2)_hR_{12}$ where R_{11} is H or C_{1-3} alkyl; h is 0, 1, 2 or 3; and R_{12} is selected from the group consisting of morpholine, pyrrolidine optionally substituted with a hydroxy or hydroxymethyl, piperidine optionally substituted with a 4-hydroxy, 4-carboxyamido or 4-aminosulfonyl group, piperazine optionally substituted on the N-atom by C_{1-3} alkyl, triazole, tetrazole, 5-mercapto-tetrazole, furan, thiophene, thiomorpholine, optionally mono or di-oxygenated on the S-atom, and amino- cyclohexane optionally substituted [on] by a hydroxy group;

- COR_{13} wherein R_{13} is a member selected from the group consisting of morpholine and piperazine optionally substituted by a C_{2-6} alkyl containing one or more [ether or] hydroxy groups;

their enantiomers and mixtures thereof, their diastereoisomers, and their pharmaceutically acceptable salts.

22. (Amended) Compound according to Claim 21 wherein:

f is 1

m is 0

X_1, X_2, X_3, X_4, are the same or different and are a member selected from the group consisting of -CONR- and -NRCO-,

where R is H or methyl,

R_1 and R_2 are the same or different, are:

$-CH_2Ar$ wherein Ar is an aromatic group selected from the group consisting of benzene, pyridine, indole, optionally substituted with up to two [residues with] substituents selected from the group consisting of C_{1-3} alkyl, [and] C_{1-3} haloalkyl, C_{1-3} alkyloxy, C_{2-4} amino alkyloxy, halogens, OH, NH_2, CN, and NR_6R_7, where R_6 and R_7, same or different, and are H or C_{1-3} alkyl;

R_3 is $-CH_2Ar_1$ wherein Ar_1 is an aromatic group selected from the group consisting of alpha naphthyl, beta naphthyl, phenyl, phenyl substituted with up to two [residues] substituents selected from the group consisting of C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3}alkyloxy, halogens, OH, and NH_2.

23. (Amended) Compounds according to Claim 22 wherein:

- X_1, X_2, X_3, X_4 are -CONH-,
- R_1 is indol-3-yl-methyl
- R_2 is phenyl-methyl optionally substituted with up to two [residues] substituents selected from the group consisting of chlorine, fluorine, CF_3, OH[,] and CN, or are selected from the group consisting of 3-pyridyl-methyl and 4-pyridyl-methyl;
- R_3 is benzyl.

25. (Amended) Compounds according to Claim 24 represented by:

i) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

ii) cyclo{Suc[1-(S)-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iii) cyclo{Suc[1-(R)-(1-methyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

iv) cyclo{Suc[1-(R)-(4-tetrahydrothiopyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

v) cyclo{Suc[1-(R)-(1-oxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

vi) cyclo{Suc[1-(R)-(1,1-dioxo-tetrahydrothiopyran-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

vii) cyclo{Suc[1-(R)-N-methyl-N-(4-tetrahydropyranyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

viii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Tyr-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

ix) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

x) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(3,5-F)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xi) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CN)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Phe(4-CF3)-[(R)-NH-CH (CH_2-C_6H_5)-CH_2NH]}

xiii) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(4-pyridyl)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xiv) cyclo{Suc[1-(R)-(4-tetrahydropyranyl)amino]-Trp-Ala(3-pyridyl)-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xv) cyclo{Suc[1-(R)-(1-methylsulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xvi) cyclo{Suc[1-(R)-(1-aminosulfonyl-piperidin-4-yl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xvii) cyclo{Suc[1-(R)-4-methyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xviii) cyclo{Suc[1-(R)-4-acetyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]} or

xix) cyclo{Suc[1-(R)-4-methylsulfonyl-piperazin-1-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}.

26. (Amended) Compounds according to Claim 23 wherein :

R_4 represents a group NR_8R_9, where R_8 is H and R_9 is methanesulfonyl, tosyl or a group $-(CH_2)_gR_{10}$, wherein g is 1 or 2 and R_{10} is morpholine, furan, or CN.

27. (Amended) Compounds according to claim 26 represented by:

xx) cyclo{Suc[1-(S)-[4]-methylsulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxi) cyclo{Suc[1-(R)-[4]-methylsulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxii) cyclo{Suc[1-(S)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxiii) cyclo{Suc[1-(R)-(4-methylphenyl)sulfonylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxiv)cyclo{Suc[1-(S)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxv) cyclo{Suc[1-(R)-2-(4-morpholino)ethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}

xxvi) cyclo{Suc[1-(R)-(2-furyl)methylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]} or

xxvii) cyclo{Suc[1-(R)-cianomethylamino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}.

30. (Amended) Compounds according to Claim 23 wherein:

R_4 represents a group COR_{13} wherein R_{13} is [a member selected from the group consisting of] morpholine[and 4-(hydroxyethyloxyethyl)-piperazine].

31. (Amended) Compounds according to claim 30 represented by:

xlvi) cyclo{Suc[1-(4-morpholino)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}[or

xlvii) cyclo{Suc[1-(4-hydroxyethyloxyethyl-piperazin-1-yl)carbonyl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2NH]}].

<u>In the Specification</u>

On page 1, line 29-32 to page 1a, line 2:

-$(CH_2)_rAr_1$ where r is 0, 1 or 2 and Ar_1 is an aromatic group chosen among: benezene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, benzoimidazole, possibly substituted with up to 2 groups chosen among: C_{1-3} alkyl, C_{1-3}haloalkyl, C_{1-3} alkyloxy and C_{2-4} amino-alkyloxy, halogens, OH, NH_2, [CN,] NR_6R_7, where R_6 and R_7 are the same or different and are H or C_{1-3} alkyl.

On page 5, lines 15-20:

R_9 is a group chosen among: 4-tetrahydropyranyl, 4-tetraiod[r]othiopyranyl, 1-oxotetraiod[r]othiopyran-4-yl, 1,1 dioxo-tetrahydrothiopyran-4-yl, N-methyl-4-piperidinyl, N-methansulfonyl-4-piperidinyl, N-aminosulfonyl-4-piperdinyl, or R_8 and R_9 together with the N atom to which they are linked represent N-methyl-piperazinyl, N-acetyl-piperazinyl, piperazinyl, N-methanesulfonyl-piperazinyl.

On page 2, lines 3-9:

R_9 is a methanesulfonyl, tosyl, tetrahydropyranyl, tetrahydrothiopyranyl possible mono or di-substituted by oxygen on the S atom, piperidyl possibly substituted on the N atom by a C_{1-3} alkyl, C_{1-3} acyl, aminosulfonyl, methanesulfonyl; or a group $(CH_2)_g$-R_{10} where $_g$ is 1,2,3 and R_{10} is chosen among morpholine, furan, CN; or R_8 and R_9 together with the N atom to which they are linked form a piperazine [possibly] optionally substituted at the other N atom [on one of its nitrogen] by C_{1-3} alkyl, C_{1-3} acyl or methanesulfonyl;

On page 30, line 31:

b) Synthesis of Boc-Trp-Phe-{(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH-[2-(4-nitro-

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